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延胡索有效成分DL-tetrahydropalmatine鎮靜作用之研究

謝明村　彭文煌

台中市　中國醫藥學院　中國藥學研究所

一、摘　要

DL－tetrahydropalmatine（THP）爲中藥延胡索（*Corydalis yanhusuo* W.T. WANG）的主要成分之一，具有鎮靜、催眠作用，其鎮靜作用機轉據劉國卿研究報告指出THP（60 mg/kg，i.p.）能降低腦部norepinephrine、dopamine、serotonin三種單胺傳遞物質的含量，並增加其代謝物的含量，而dopamine的甲氧基代謝物3－methoxyltyramine含量明顯減少，大劑量的pargylin（75mg/kg，i.p.）及reserpine（2.5mg/kg）能改變THP對腦部紋狀體及邊緣系統內三種單胺傳遞物質的含量，故劉氏推論THP之鎮靜作用爲一種短效單胺排空劑，然劉氏並無探討THP對於腦內dopamine接受器功能之影響，因此本研究擬以行爲藥理學、生物化學及伏安法（voltammetry）測定法，併用dopamine接受器的致效劑或拮抗劑，探討其作用機轉、作用部位。

研究結果顯示，THP隨劑量的增加而可明顯抑制大鼠的自發運動量，在較大劑量（20 mg/kg）下並有僵硬症（rigidity）產生，THP（10mg/kg，i.p.）可抑制兒茶酚胺合成抑制劑α－MT、排空劑reserpine、D_1 及 D_2 混合拮抗劑haloperidol、D_2 拮抗劑sulpiride、serotonin前驅物質5－HTP、GABAB致效劑baclofen所誘發之運動量抑制作用，並能抑制dopamine前驅物質L－dopa併用dopa decarboxylase抑制劑benserazide、D2致效劑apomorphine、膽鹼阻斷劑scopolamine、serotonin合成抑制劑PCPA所誘發之運動量增加作用，顯示THP之鎮靜、催眠作用可能與腦內單胺神經系統及GABAergic系統有關。

以生物化學方法（HPLC）探討THP對於大鼠腦內單胺濃度之影響，結果顯示，THP隨劑量之增大可明顯降低大腦皮質（cortex）及腦幹（brain stem）中norepinephrine及dopamine的濃度並增加dopamine代謝物HVA的濃度，在較大劑量（20mg/kg，i.p.），並可降低皮質中5－HT的濃度及增加其代謝物5－HIAA的濃度，由此顯示，THP之鎮靜、催眠作用可能與降低大腦皮質及腦幹中dopaminergic系統的活性有關，其較大劑量所產生之僵硬症可能與THP抑制皮質及腦幹中dopamine及降低皮質中5－HT的濃度有關。

以伏安法（voltammetry）探討THP對於清醒大鼠腦部紋狀體（corpus striatum）中dopamine釋放量的影響，結果顯示，低劑量THP可明顯增加活體大鼠腦部紋狀體中dopamine的釋放，且隨劑量之加大而增強，又因THP能抑制腦部dopamine系統的功能，由此更顯示，THP之鎮靜、催眠作用主要是作用在腦部紋狀體中dopamine神經元，阻斷突觸後dopamine接受器，並回饋性的作用於突觸前D2接受器而增加dopamin的釋放。

綜合以上結果，顯示THP之鎮靜、催眠作用及僵硬症的產生主要是作用於紋狀體與黑質中dopamine－acelycholine－GABA－dopamine神經環路，主要是作用在腦部紋狀體中dopamine神經元，阻斷突觸後dopamine接受器，並回饋性的作用於突觸前D2接受器而增加dopamine的釋放（release）。且僵硬症的產生亦受到5－HT的調節。

二、緒　言

近年來，由於我國經濟突飛猛進，工商業發達，造成競爭激烈，使得焦慮、失眠的患者激增。焦慮、失眠直接或間接影響身體的健康，進而降低工作效率，這些問題不僅是當代醫學之難題，也是現代社會問題之一環。臨床上常用之鎮靜、安眠藥如barbiturates、benzodiazepines等藥物，在治療上頗具效果，然而其被濫用之情形及思睡、疲倦、眩暈、反應遲頓及依賴性等副作用[1]，業已到不容忽視的地步。因此，尋找有效而無副作用之鎮靜安眠藥，爲當前之要務。

延胡索爲罌粟科植物*Corydalis yanhusuo* W. T. WANG之乾燥塊莖，最早著錄於開寶本草，性味辛、苦、溫，歸肝、胃經。主破血，產後諸病，因血所爲者，婦人月經不調，腹中結塊，崩中淋露，產後血運，暴血衝上，因損下血，功能活血去瘀，理氣止痛。本草綱目記載：「活血、利氣、止痛」，綱目發明曰：「能行血中氣滯，氣中血滯，故專治上下一身諸痛，用之中的，妙不可言」[2]，自古用於淨血、鎮痛、鎮痙，其別名有元胡、玄胡、玄胡索等，現今中醫藥界通稱爲元胡，並用爲一種止痛要藥。

延胡索屬（Corydalis）植物約有兩百種，主產歐、亞兩洲，尤以中國大陸爲最多，市場上延胡索藥材的主要來源有五種：(1)延胡索，(2)東北延胡索，(3)齒瓣延胡索，(4)全葉延胡索，(5)土延胡索，主要以塊莖供藥用，已分離出近二十種成分，分屬於原小檗鹼類及原阿片鹼類生物鹼，四氫巴馬汀（tetrahydropalmatine）爲其有效成分之一，具有旋光性，其左、右旋異構物的作用不同，左旋具有鎮痛、鎮靜作用，爲中樞抑制劑，較大劑量則會產生僵硬症（rigidity），右旋體反有短時興奮作用，爲dopamine的排空劑。

幾年來承蒙國科會經費輔助從事延胡索有效成分對於中樞神經系統之影響，研究結果獲得從延胡索中分離出五種protoberberine type生物鹼：(1)(－)－tetrahydrocoptisine，(2)(＋)－corydopamineline，(3)(±)－tetrahydropalmatine，(4)(－)－tetrahydrojatro-rrhizine，(5)(±)－palmatine，其中dl－tetrahydro－palmatine（THP）具有鎮靜、催眠、鎮痛[3]、降壓[4]、抗心律不整[5]及抗甲狀腺機能亢進症[6]等作用，其鎮靜、催眠作用

機轉據劉國卿研究報告指出THP（60 mg/kg，i.p.）能降低腦部NE、dopamine、serotonin三種單胺傳物質的含量，並增加其代謝物的含量，而dopamine的甲氧基代謝物3－methoxyl－tyramine含量明顯減少[6]，大劑量的pargylin（75 mg/kg，i.p.）[7]及reserpine（2.5 mg/kg，i.p.）[8]能改變THP對腹部紋狀體及邊緣系統內三種單胺傳遞物質含量的影響，故劉氏推論THP之鎮靜作用爲一種短效單胺排空劑[3]，然劉氏並無探討THP對於腦內dopamine接受器功能之影響，因此本研究擬以自發運動量、腦內單胺濃度及伏安法（voltammetry）測定法，併用dopamine接受器的致效劑或拮抗劑，探討其作用機轉、作用部位。

三、實驗之部

實驗材料

㈠實驗藥材之製備：

本實驗所使用之藥材經鑑定爲罌粟科Papaveraceae植物延胡索*Corydalis yanhusuo* W. T. Wang的塊莖。

本實驗藥材之抽取製備及純化，係由靜宜女子大學理學院院長賴貞秀博士及應用化學研究所所長黃克峰博士負責（抽取流程如圖一），且再運用分配分離法，分別得到延胡索甲醇層、正丁醇層、水層及氯仿－A層、氯仿－B層等五層。並由氯仿－B層以管柱層析法(Column Chromatograph)分離出protoberberine type alkaloids，經純化得dl－tetrahydropalmatine（THP）供作本實驗，實驗材料料以磷酸10％（V／V）與蒸餾水（1：9）混合製備，以1 N氫氧化鈉調至pH值4.5。

㈡實驗試藥

1. α－Methyl－p－tyrosine methyl ester HCl (α－MT), 5－Hydroxytryptophan (5－HTP), dl－p－Chlorophenylamine (PCPA), Norepinephrine HCL (NE), Dopamine HCl (DA), 5－Hydroxytryptamine HCl (5－HT), Vanilylmandelic acid (VMA), Homovanillic acid (HVA), 5－Hydroxyindole－3－acetic acid (5－HIAA), Haloperidol（溶於lactic acid）, Baclofen, Muscimol, Apomorphine（溶於ascorbic acid）, sulpiride（溶於0.1 N HCl）, Scopolamine，reserpine（溶於glacial acetic acid）皆購自Sigma公司。

2. Levo－dopa（日本協和發酵），Benserazide（Hoffman－La Roche）。

㈢實驗動物

本研究所使用動物爲：

Sprague－Dawley系雄性大鼠，體重200～250公克（自發運動量實驗用）及250～300公克（腦內單胺濃度測定及活體電位化學測定實驗用）。

四、實驗方法

㈠對自發運動之影響

運動量之測定是使用動物運動量測定裝置（MK－ANIMEX Activity Meter Model SE, Muromachi Kikai Co.，Ltd. Japan），敏感度定爲35μA，記錄大鼠經腹腔注射給予不同劑量的THP後之各種活動行爲的變化（包括走動、站立、整飭、嗤鼻等）。5分鐘後放入測定裝置內適應5分鐘再開始記錄，觀察並連續記錄2小時，每組6隻。實驗時爲上午八時至下午六時。對照組給Saline。

㈡對改變腦內catecholaminergic system之物質所引起自發運動之影響

將THP（10mg/kg，i.p.）10分鐘前給予，再與下述物質分別併用，依前法（方法一），于測定前5分鐘將大鼠移入運動量測定裝置適應，待5分鐘後開始記錄，觀察並連續記錄2小時，對照組給saline。

本實驗所使用於改變腦內catecholaminergic system物質的劑量及時間分別爲：L－dopa（200mg/kg, i.p.）50分鐘前給藥，加上Benserazide（50 mg/kg, i.p.）80分鐘前給藥，二者均需於使用前新鮮配製[9]；α－MT（50mg/kg, i.p.）2小時前處置[10]；reserpin（0.5mg/kg, i.p.）18小時前給藥[11]。

㈢對改變腦內serotonergic system之物質所引起自發運動之影響

將THP（10mg/kg, i.p.）10分鐘前給予，再與下述物質分別併用，依前法（方法一），于測定前5分鐘將大鼠移入運動量測定裝置適應，待5分鐘後開始記錄，觀察並連續記錄2小時。對照組給saline。

本實驗所使用於改變腦內serotonergic system物質的劑量及時間分別爲：5－HTP（50 mg/kg, i.p.）30分鐘前給藥[12]；PCPA（200 mg/kg, i.p.）24小時前給藥[13]。

㈣對改變腦內GABAergic system之物質所引起自發運動之影響

將THP（10mg/kg, i.p.）10分鐘前給了，再與下述物質分別併用，依前法（方法一），于測定前5分鐘將大鼠移入運動量測定裝置適應，待5分鐘後開始記錄，觀察並連續記錄2小時。對照組給saline。

本實驗所使用於改變腦內GABAergic system物質的劑量及時間分別爲：
baclofen（0.5mg/kg, i.p.）10分鐘前給藥[14]；muscimol（0.5mg/kg, i.p.）10分鐘前給藥併用[15]。

㈤ 對改變腦內dopaminergic system之物質所引起自發運動之影響

將THP以不同劑量10分鐘前腹腔注射給予，再與下述物質分別併用，依前法（方法一），于測定前5分鐘將大鼠移入運動量測定裝置適應，待5分鐘後開始記錄，觀察並連續記錄2小時。對照組給saline。

本實驗所使用於改變腦內dopaminergic system物質的劑量及時間分別爲：

apomorphine（1mg/kg, s.c.）15分鐘前給藥[16]，haloperidol（0.001 mg/kg，i.p. 30分鐘前給藥[17]，sulpiride（20 mg/kg, i.p.）30分鐘前給藥[18]，scopolamine（0.5 mg/kg, i.p.）30分鐘前給藥[19]，均需於使用前新鮮配製。

㈥ 對大鼠腦內單胺及其代謝物濃度之影響

本實驗使用體重250～300公克雄性大鼠，每組6隻，經腹腔注射THP（10, 20 mg/kg）10分鐘後，將大鼠斷頭，取出全腦，取出皮質及腦幹，分別置於碎冰中，分離流程如圖二[20]，在5ml 0.001N HCl與500μl 0.1M EDTA下以均質機研勻之，加入4g NaCl，並以12ml n－butanol抽取，經振盪離心後，取得n－butanol層，再加入17m1 n－heptan與400μl 0.025 N酸性溶液振盪之，則單胺移入酸入酸性水溶液層。上述餘留n－heptane層續以200μl 0.2 M Tris－HCl鹼性緩衝溶液（pH爲8.5）振盪抽取並離心，可得單胺代謝物。對照組給saline。以上分離所得腦內單胺（NE，DA，5－HT）及其代謝物（HAV, VAM, 5－HIAA），以外標法測定之。使用高速液態層析儀（HPLC model 440, Solvent Delivery system M45）（Waters Associates）及檢出器（Electrochemical Detectors LC－4B）（Bioanalytical system Inc.）測定之。分離所用Column爲Lichrospher 100（RP－18 endcapped, 4mm x125mm）（E. Merck 50734），移動相爲加有PIC B7（Waters Associates）之methanol/Water（測定單胺濃度時爲7：93，測定代謝物濃度時爲2：98），其流速爲2.0ml/min。分離溶出物面積係使用Data module M746（Waters）型記錄之。

㈦ 對活體清醒大鼠腦內單胺電位化學變化之影響

1. 電極製備：

將單一碳纖維（直徑12um，AVCO，Lowell，MA）插入已拉成形的玻璃微滴管（pipete，20－25公釐長度）之內。使用精細的剪刀切除pipette的頂口，纖維輕輕的接合玻璃頂口的內部，然後將炭纖維由pipette頂口拉出，內灌銀漿使纖維通電。pipettee的頂和鈍的尾端用cyanoacrylate（超著膠）黏著劑封口，整個表面均爲厚約12um，長約500um的pyrolytic炭纖維表面。

2. 碳纖維電極處理：

爲了改良碳纖維對於單胺的敏感性及選擇性，電極須依Gonon及其研究同仁發表的白

皮書改良的方法作電的前處理[21]，修正後的電前處理包括兩個步驟：

第一、將電極放入0.1M硫酸溶液中通以直流電2.2伏特30秒。

第二、再將電極放入IN鹽酸溶液中以2.2伏特直流電通電30秒。碳纖維電極須以蒸餾水洗滌。

3. 電極外層黏附Nafion：

經過上述前處理碳纖維電極，把電極的頂端浸入Nafion溶液中（5%溶液10 ul，Aldrich Chemical Company Inc，Milwaubel，Wis. USA）之內3分鐘。然後將覆蓋上一層Nafion的碳纖維電極在攝氏60度乾燥20秒，重覆乾燥3次，再將黏附好Nafion之電極置於3M氯化鈉溶液中，測其電容及電阻，只有電容值約等於0.039uF，而電阻值在200－400歐姆的電極才可供實驗使用[22]。本實驗使用法國TACUSSEL公司的Biopulse系統在離體及活體實驗中放出不同的脈衝電流來測定單胺的氧化電位，其可提供DPV、DNPV、DPA三種測量方式，目前我們使用的是DPA（differential pulse amperometry）法，其設定參數如下：

Pi（imposed initial potential）＝－220 mV

Pf（imposed final potential）＝70 mV

T（pulse cycle）＝2s

tl（prepulse）＝70 ms； t2（measuring pulse）＝40 ms

△V（measuring pulse potential）＝40 mV。

4. 離體實驗過程：

首先將經過Nafion黏附的碳纖維電極置於含磷酸緩衝溶液的小燒杯中，以水浴控制溫度在37℃，然後加入一定量的多巴胺來進行較準，爲提高實驗的準確度，每次實驗用的多巴胺溶液均需新鮮配製，用磷酸緩衝食鹽水（0.1M，pH 7.4）當空白試驗溶液及溶劑。每測試濃度的電位圖均記錄2次，每次從最低濃度（200 nM）逐漸增加到最後濃度（400nM）。磷酸緩衝溶液組成成分爲KCl 10.2g/l，KH_2PO_4 0.2g/l，NaCl 8g/l，Na_2HPO_4 1.44g/l。

5. 活體內多巴胺的量測過程：

將重250～300公克的雄性Sprague－Dawley大鼠以urethane（1.5g/kg，腹腔注射）麻醉，將其頭部固定於立體定位儀上，依照Paxinos和Watson座標，將塗上一層Nafion的碳纖維電極植入層狀體（A/P：bregma往前0.2mm，M/L：中線左、右旁開3.0mm，D/V：骨表面下5.5mm）[23]及附加的參考（Ag/AgCl）電極置於皮質骨腔壁區域的硬膜（dura）表面上。差異脈衝電位圖（voltammograms）每0.2秒自動地記錄，在每個實驗結束，拿出電極後，必須校準一次。若欲確認電極位置正確與否，可供應一連續的5伏特直流電3秒鐘，執行電極損害。通過電極的電流大約0.4nA。再將腦解剖，冰凍並保持在零下20度，腦幹切成20um冠狀的薄切片，收集第三節作Nissl's染色。在碳纖維位置附近的損害面積大約直徑200um和長約500um。當碳纖維電極在活體實驗後被標化，植

入另一電極於相同位置作電的破壞。

6. 統計學分析：

本實驗之數據，以Student's T－test方法及ANOVA方法統計，分析其間差異的顯著性，凡P值小於0.05以下時，則認爲有統計意義。

五、實驗結果

㈠對自發運動之影響

如圖三所示，腹腔注射給了不同劑量（5, 10, 20mg/kg）的THP對大鼠的自發動量有抑制作用，且隨劑量之增大而增強。當給予20mg/kg劑量時，大鼠則有明顯的僵硬症（rigidity）產生。

㈡對改變腦內catecholaminergic system之物質所引起自發運動之影響

1. 如圖四所示，α－MT（100mg/kg, i.p.）單獨給予時可使大鼠自發運動量減少；與THP（10mg/kg, i.p.）併用後，其運動量抑制作用更顯著的被抑制（$p<0.01$）。

2. 如圖五所示，L－dopa（200mg/kg, i.p.）併用benserazide（50mg/kg, i.p.）可使大鼠自發運動量顯著的增加，當與THP（10mg/kg, i.p.）併用後，對於其運動量的興奮作用有明顯的抑制作用（$p<0.01$）。並可抑制L－dopa＋benserazied所誘發之攻擊性行爲。

3. 如圖六所示，reserpine（0.5mg/kg, i.p.）單獨給藥，對大鼠的自發運動量有明顯的抑制作用，當與不同劑量的THP併用後，其運動量有顯著抑制（$p<0.05$）：當與THP（1mg/kg, i.p.）併用後，對其運動量抑制作用無影響。

㈢對改變腦內serotonergic system之物質所引起自發運動之影響

1. 如圖七所示，5－HTP（50mg/kg, i.p.）單獨給藥可使大鼠自發運動量顯著減少，當併用THP（10mg/kg, i.p.）後，其運動量更顯著的降低（$p<0.01$）。

2. 如圖八所示，PCPA（200mg/kg, i.p.）單獨給藥時，可顯著增加大鼠的自發運動量，當與THP（10mg/kg, i.p.）併用後，對此自發運動量增加現象有明顯的抑制作用（$p<0.01$）。

㈣對改變腦內GABAergic system之物質所引起自發運動之影響

1. 如圖九所示，單獨給予baclofen（0.5mg/kg, i.p.）可明顯抑制大鼠的自發運動量，當與THP（10mg/kg, i.p.）併用後，對其自發運動量抑制作用更加抑制。

2. 如圖十所示，單獨給予muscimol（0.5mg/kg, i.p）可明顯抑制大鼠的自發運動

量，當與THP（10mg/kg, i.p.）併用後對其自發運動量抑制作用並無影響。

㈤對改變腦內dopaminergic system之物質所引起自發運動之影響

1. 如圖十一所示，haloperidol（0.001mg/kg, i.p.）單獨給予時可使大鼠自發運動量減少；與THP（10mg/kg, i.p.）併用後，其運動量更顯著的被抑制（$p<0.01$）。

2. 如圖十二所示，單獨給予scopolamine（0.5ml/kg, i.p.）可使大鼠自發運動量顯著的增加，當與THP（10mg/kg, i.p.）併用後，對於其運動量的興奮作用有明顯的抑制作用（$p<0.01$）。

3. 如圖十三所示，sulpiride（20mg/kg, i.p.）單獨給藥，對大鼠的自發運動量有明顯的抑制作用，當與THP（10mg/kg, i.p.）併用後，其運動量更加抑制；當與THP（1 mg/kg, i.p.）併用後，對其運動量抑制作用無影響。

4. 如圖十四所示，apomorphine（1 mg/kg, i.p.）單獨給藥，對大鼠的自發運動量有明顯的興奮作用，當與THP（10mg/kg, i.p.）併用後，對其運動量與興奮作用有顯著的抑制作用，並可抑制其所誘發之旋轉活動；當與THP（1 mg/kg, i.p.）併用後，對其運動量抑制作用無影響。

㈥對大鼠腦內單胺及其代謝物濃度之影響

如表一、表二所示，不同劑量THP（10、20mg/kg, i.p.）可顯著降低大鼠大腦皮質及腦幹中NE及DA的濃度，增加DA代謝物HVA的濃度，並顯著增加DA的轉換速率；20 mg/kg劑量的THP可顯著降低大腦皮質中5－HT的濃度，增加其代謝物5－HIAA的濃度，並增加其轉換速率。

㈦對活體清醒大鼠腦內單胺電位化學變化之影響

如圖十五所示，低劑量THP（1, 5mg/kg, i.p.）對於大鼠腦部層狀體（corpus striatum）dopamine的釋放有明顯的增加作用，且隨劑量的增加，增加作用隨之增強。

六、討　論

精神病的病因有二：一爲中樞神經系統內含dopamine的神經細胞功能過度活動，產生過多的dopamine，作用於其接受器上而引起精神病，二爲甲基化的indoleamine衍生物（如LSD，mescaline等）在體內有異常的積聚時，它們僞裝成假性傳導物質（false－neurotransmitter），作用於dopamine接受器上而誘發精神病。

臨床上使用之精神病治療劑（neuroleptics）被認爲有效的原因是因爲它們能夠作用於腦中dopamine系神經細胞突觸及其接受器，阻斷腦部DA接受器[24]、增加DA的轉換速率[25－27]或DA的釋放（release）[28]，如chloropromazine，haloperidol等。並可降低任

何實驗動物的自發運動量[29]，拮抗定型活動及旋轉活動[30,31]，但會誘發錐體外症狀副作用（如僵硬症）[32]。

本實驗首先探討THP對大鼠自發運動量之影響，由實驗結果顯示，THP對大鼠自發運動量有抑制作用，且會隨著劑量之加大而增強，其ED50爲7.4mg/kg。在較大劑量（20 mg/kg）則會產生顯著僵硬症，且THP能明顯抑制DA致效劑apomorphine所誘發的定型旋轉活動，也能拮抗l－dopa加benserazide所誘發之攻擊性行爲，顯示其可能爲一種精神病治療劑，具有阻斷腦內DA接受器的功能。因此，本實驗接著併用一些能改變腦內單胺系統、GABAergic系統的物質，探討THP對這些物質所引起之自發運動量變化的影響，來闡明THP之鎮靜、催眠機轉。

爲進一步探討THP與腦中樞catecholaminergic system之關係，故併用catecholaminergic system之活性增強劑——L－dopa加benserazide，或活性抑制劑——α－methyl－p－tyrosine（α－MT），來探討THP對其所引起自發運動量變化之影響。首先benserazide爲catecholamine合成途徑中dopa decarboxylase抑制劑，能阻斷dopa脫去carboxyl group，以阻止dopa之分解。又因dopamine不易通過血腦障壁（blood－brain－barrier），但其前驅物L－dopa則易通過血腦障壁，進入腦部後再轉成dopamine，而增強catecholaminergic system的活性，故benserazide併用L－dopa時會增加L－dopa進入腦部的濃度而增強catecholaminergic system之活性，而顯著的誘發運動量增加並會誘發攻擊性行爲(aggressive behaviors)[10]：當THP與L－dopa加benserazide併用，其所誘發的自發運動量興奮作用，即被THP所抑制，同時THP對benserazide加L－dopa所誘發攻擊性行爲（aggressive behaviors）也有抑制現象。其次α－MT及catecholamine合成途徑中tyrosine hydroxylase的抑制劑，α－MT能阻斷tyrosine轉化爲dopa而干擾catecolamin(NE、DA)之合成，會減低catecholaminergic system之活性，而使大鼠自發運動量減少[11]。THP能增強α－MT對運動量之抑制作用。Reserpine降低自發運動量主要作用於紋狀體及Nucleus accumbens[33]，主要是阻斷D_1接受器[34]，而產生運動量抑制作用，THP與reserpine併用後，對reserpine所產生之運動量抑制作用，有更明顯的抑制。Haloperidol爲一種精神病治療劑，屬DA接受器的阻斷劑，可阻斷DA系統的活性而使運動量降低[35]，sulpiride亦爲一種精神病治療劑，屬D_2接受器阻斷劑，大劑量時可阻斷DA神經原的突觸後D_2接受器，亦可阻斷DA系統的活性而使運動量降低[36,39]，THP與haloperidol或sulpiride併用後，對haloperidol或sulpiride所誘發之運動量抑制作用有顯著的抑制，又apomorphine爲D_2接受器致效劑[40]，較大劑量下可增加大鼠自發運動量[40,44－49]及旋轉活動[47]，THP與apomorphine併用後，對apomorphine所誘發之自發運動量增加有顯著的抑制，由以上結果顯示THP具有降低中樞dopaminergic system之活性，同時又具有antiaggressive behaviors作用。再由THP對腦內單胺及其代謝物濃度之影響的實驗結果顯示，THP可顯著降低NE及DA在大腦皮質及腦幹之濃度，並且明顯的增加DA代謝物HVA在大腦皮質及腦幹之濃度，此兩部位

HVA與DA的比值亦明顯增大，顯示其轉換速率增加，且隨劑量的加大，作用隨之增強，由於DA在大腦皮質及腦幹爲興奮性傳遞物質[49,50]，因此THP抑制中樞dopaminergic system活性及antiagressive behavior之作用，可能與降低腦內DA神經內DA濃度並增加其轉換速率有關。

再探討THP與serotoninergic system的關係，因腦內serotonin與catecholamine之間有某種關係存在，支配伏膈核及海馬等腦區的DA神經末稍是受5－HT神經纖維的抑制性控制，並與自發運動有密切關聯[51－53]，可影響catecholamine所引起的各種行爲。故併用serotonergic system之活性抑制劑——PCPA或活性增強劑——5－HTP，來探討THP對其所引起自發運動量變化之影響。PCPA乃serotonin合成途徑中tryptophan hydroxylase的抑制劑，當投予PCPA會使腦中5－HT的濃度降低，使DA神經原脫抑制，動物出現自發運動量亢進現象[14,54]，這種作用可因投予serotonin之前驅物質5－HTP所反轉，5－HTP乃serotonin之前驅物質，能提高中樞serotonin的含量，使自發運動量減少[31]。THP在較小劑量（10mg/kg）時，可顯著拮抗PCPA所造成catecholamine增加之運動量增加，並增強投予5－HTP所引起運動量減少的作用，但5－HTP對THP所誘發之運動量抑制並無影響，且對於大腦皮質及腦幹中5－HT及其代謝物的含量亦無影響，可能是THP阻斷DA神經原功能的結果。THP在較大劑量（20mg/kg）下，可顯著降低5－HT在大腦皮質之濃度，並且明顯的增加其代謝物5－HIAA在大腦皮質之濃度，5－HIAA與5－HT的比值亦明顯增大，顯示其轉換速率增加，在紋狀體，僵硬症的產生與dopaminergic及serotonergic system的活性低下有關[55,56]，因此THP降低皮質中5－HT的濃度及增加其轉換速率與僵硬症的產生有間接關係。

Scopolamine具有中樞cholinergic功能的拮抗作用，會誘發自發運動量的增加，且隨DA系統功能的增強而增強，隨DA系統功能減弱而減弱[20,57－59]。THP與scopolamine併用後，對scopolamine所誘發之自發運動量增加有顯著的抑制作用，在紋狀體內cholinergic神經原爲黑質－紋狀體DA徑路的跟隨神經原，有突觸後接受器位於cholinergic神經原上，並經由該接受器施予緊張性抑制作用[60－62]，當DA突觸後接受器的功能受阻斷後，cholinergic神經脫抑制，cholinergic神經活性增強，然THP之l－form異構物不能與muscarinic接受器相結合[65]，間接排除THP直接阻斷muscarinic接受器的可能性，因此，THP抑制scopolamine所誘發之自發運動量增加，可能是THP阻斷DA系統功能所致的一個輔助證據。

爲進一步探討THP與GABAergic systm的關係，因此將THP與GABAA致效劑muscimol或GABAB致效劑baclofen併用，因爲在紋狀體中，GABA控制DA的功能[64－66]，DA存於黑質紋狀體神經終端[67]，GABA存於紋狀體投射神經的神經軸突的側支[68]及環狀神經[69]，GABA是藉由調節DA的釋放而控制DA，GABAA接受器參與DA釋放的興奮[70,71]，而GABAB接受器則參與DA釋放的抑制[72,73]，GABAB接受器位於DA神經終端，紋狀體中DA神經去極化而使tyrosine hydroxylase活化須要鈣離子的存在，去極化

可打開電位依賴性的鈣離子通道（Voltage－dependent calcium channels）而使鈣離子進入DA神經終端，baclofen活化GABAB接受器而阻斷神經終端因去極化所誘發之鈣離子的增加[74,75]，進而抑制tyrosine hydroxylase的活化[76]，又dopamine在紋狀體中則經由D2接受器抑制性的調節紋狀體GABA神經原中GABA的釋放[77]，THP與baclofen併用後，對於GABAB致效劑baclofen所誘發運動量抑制作用有顯著的抑制，可能爲THP阻斷紋狀體DA系統，而使GABA神經原脫抑制的結果，GABAB致效劑與THP有協同的作用。

綜合以上結果，可知THP的鎮靜、催眠作用機轉與阻斷腦部紋狀體DA神經突觸前及突觸後接受器的功能有密切的關係，且THP在較大劑量會有僵硬症產生，THP可能爲一種精神病治療劑。黑質紋狀體系統中存有突觸前D_2自動接受器及突後D_2接受器[78]，其內生性dopamine的釋放則受突觸前D_2接受器的調節[64,79]，典型精神病治療劑在低劑量時作用於DA神經突觸前接受器而增加DA的代謝及釋放[80,81]，爲進一步探討THP是否有相同的作用，故以活體電位測定法（Voltammetry）探討THP對於大鼠腦部紋狀體DA中釋放量的影響，結果顯示，低劑量THP可明顯增加大鼠腦部紋狀體中DA的釋放，且隨劑量之加大而作用增強，由此顯示，THP之鎮靜、催眠作用主要是作用在腦部紋狀體DA中神經元，阻斷突觸後DA接受器，並回饋性阻斷突觸前D_2自動接受器對DA釋放的抑制，而使dopamine的釋放增加。

綜合以上結果，顯示THP之鎮靜、催眠作用及僵硬症的產生主要是作用於紋狀體與黑質中DA－ACH－GABA－DA神經環路，阻斷突觸後的DA接受器，並回饋性阻斷DA神經終端突觸前D_2自動接受器對DA釋放的抑制，使dopamine的釋放增加。僵硬症的產生可能也與抑制serotoninergic system的活性有關。THP可能爲一種精神病治劑（neuroleptics）。

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Table 1. Means ± SE values for concentration (ng/kg) of monoamines and its metabolites in the cerebral cortex of rats after acute treatment with dl-tetrahydropalmatine (10, 20 mg/kg; i.p.).

Treatment	cerebral cortex								
	NE (ng/g)	VMA (ng/g)	VMA/NE	DA (ng/g)	HVA (ng/g)	HVA/DA	5-HT (ng/g)	5-HIAA (ng/g)	5-HIAA/5-HT
0.9 % saline	2567±305	325±19	0.127	2240±307	316±24	0.141	1079±72	424±17	0.393
THP (10 mg/kg, i.p.)	1663±91**	341±27	0.205	1520±172*	440±42*	0.300	867±56	499±46	0.576
THP (20 mg/kg, i.p.)	981±80**	380±24	0.388	368±78**	501±34**	1.363	663±84**	596±42**	0.900

Data presented as the mean ± S.E. of 5-6 rats for each group.

* significantly different from the control value (saline group), $p < 0.05$ (as compared with the control group by ANOVA following Duncan's multiple range test).

** significantly different from the control value (saline group), $p < 0.01$ (as compared with the control group by ANOVA following Duncan's multiple range test).

Table 2. Means ± SE values for concentration (ng/kg) of monoamines and its metabolites in the brain stem of rats after acute treatment with dl-tetrahydropalmatine (10,20 mg/kg; i.p.).

Treatment	brain stem								
	NE (ng/g)	VMA (ng/g)	VMA/NE	DA (ng/g)	HVA (ng/g)	HVA/DA	5-HT (ng/g)	5-HIAA (ng/g)	5-HIAA/5-HT
0.9 % saline	2389±144	353±12	0.148	3666±373	370±26	0.101	794±60	315±47	0.398
THP (10 mg/kg, i.p.)	1669±116**	350±13	0.210	1031±209*	483±34*	0.469	681±32	338±27	0.496
THP (20 mg/kg, i.p.)	1315±98**	374±13	0.284	700±45**	557±36**	0.796	654±52	380±45	0.581

Data presented as the mean ± S.E. of 5-6 rats for each group.

* significantly different from the control value (saline group), $p < 0.05$ (as compared with the control group by ANOVA following Duncan's multiple range test).

** significantly different from the control value (saline group), $p < 0.01$ (as compared with the control group by ANOVA following Duncan's multiple range test).

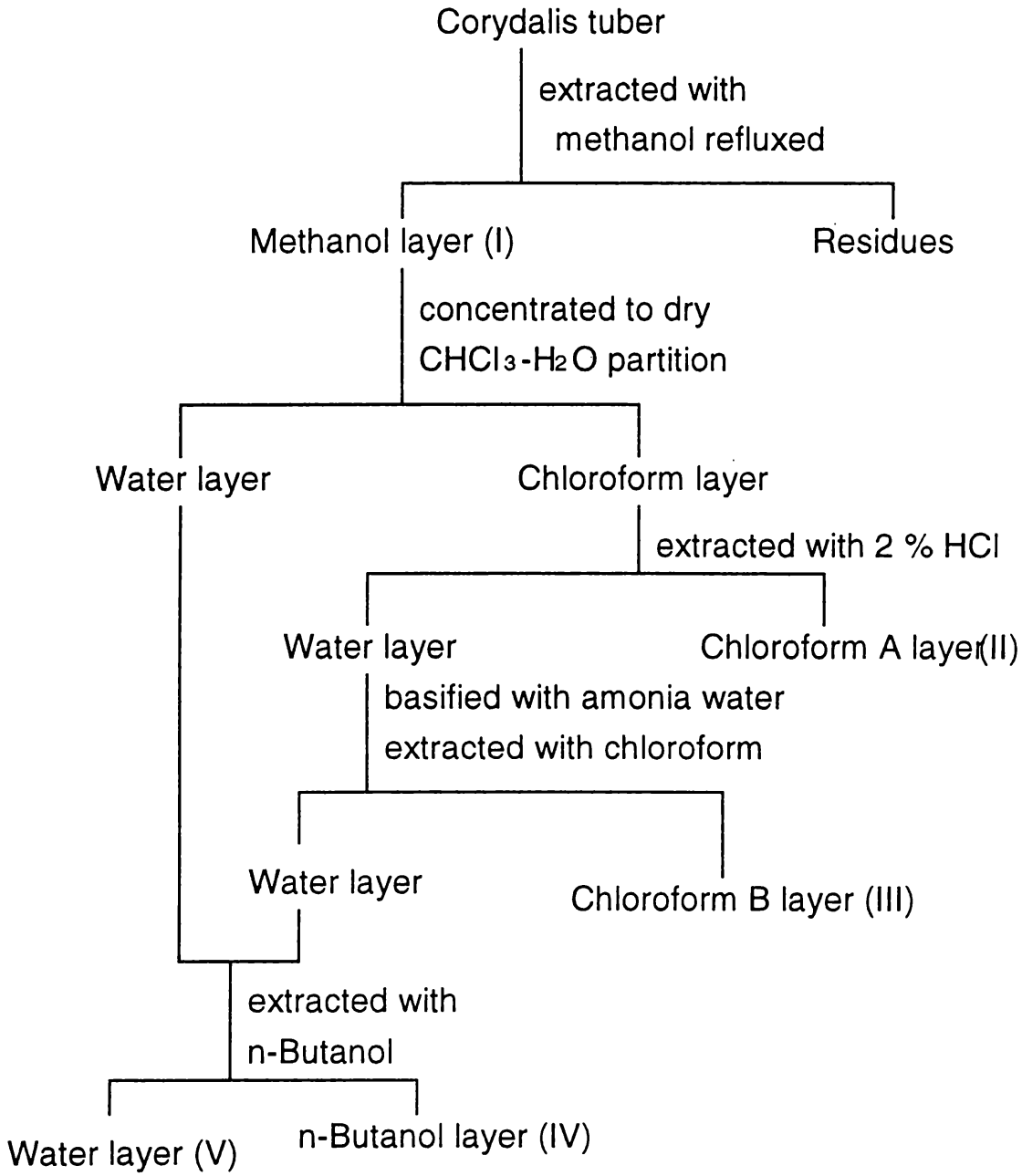

Fig 1. Separation of Corydalis tuber.

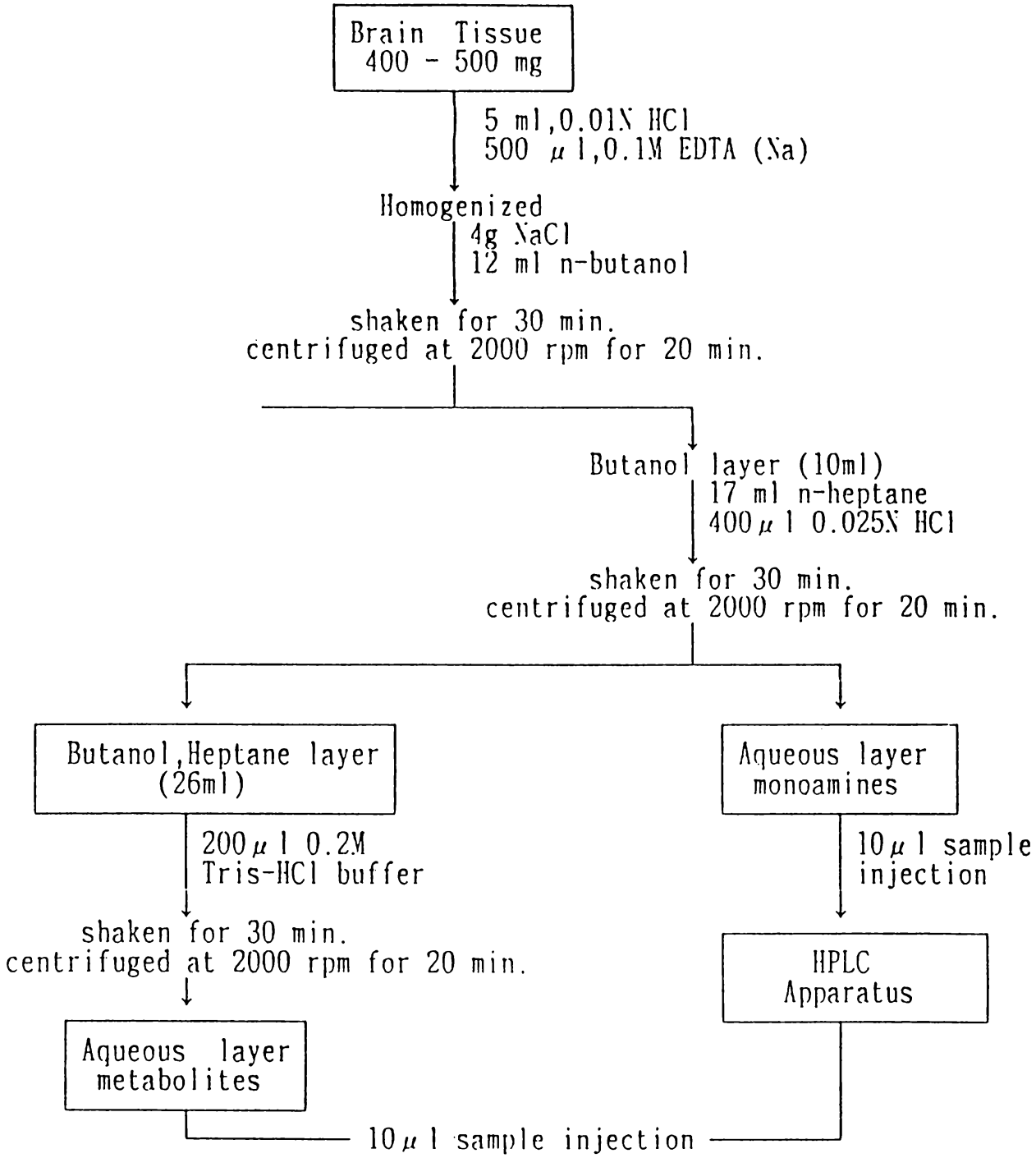

Fig 2. Brain tissue cleanup method before HPLC biogenic monoamines and metabolites analysis.

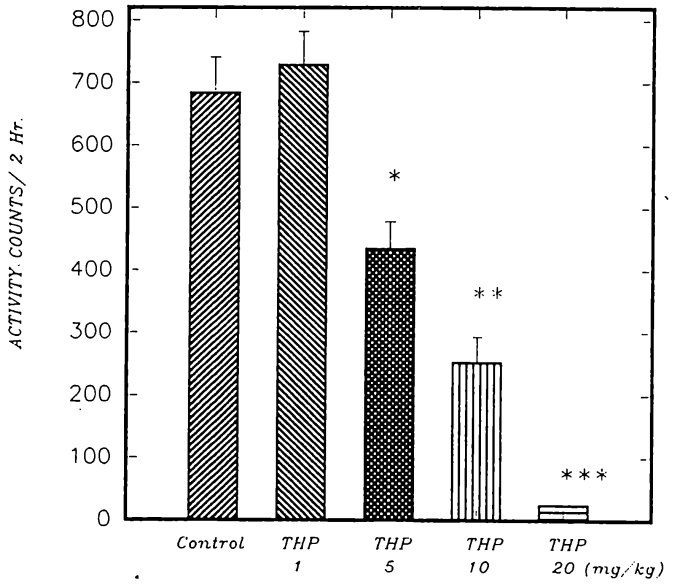

Fig 3. Effect of intraperitoneal injection of dl－tetrahydropalmatine on the locomotor activity in rats. Data are presented as group means ±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (1,5,10,20 mg/kg, 10 mins prior to testing).* significantly different from control group (*$p<0.05$,** $p<0.01$, *** $p<0.001$, Duncan's multiple range test).

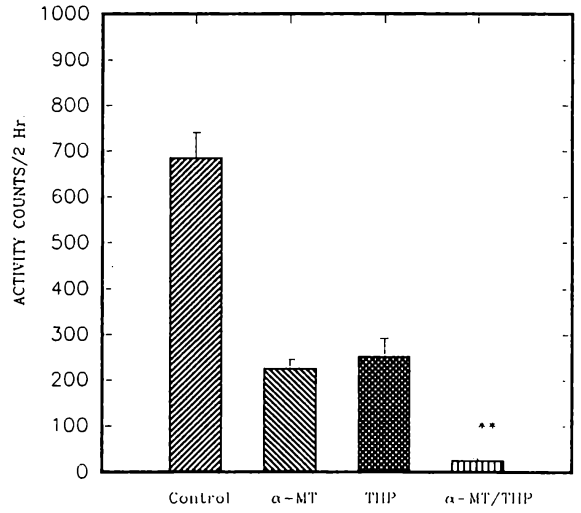

Fig 4. Effect of dl－tetrahydropalmatine on the locomotor activity produced by α－MT in rats. Data are presented as group means±SE of 6 for each group. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), α－MT ＝α－methyl－P－tyrosine (50 mg/kg, 2 hrs prior to testing), α－MT/THP＝ α－methyl－p－tyrosine pretreatment plus dl－tetrahydropalmatine.** significantly different from α－MT group ($p<0.01$, Duncan's multiple range test).

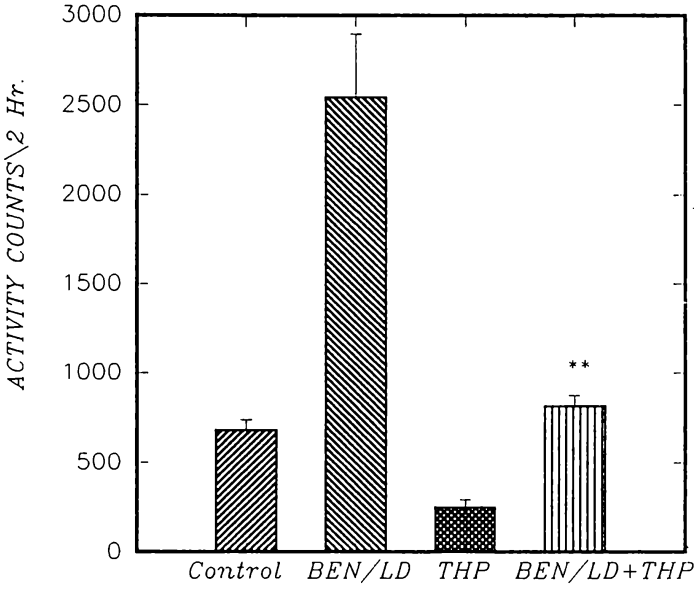

Fig 5. Effect of dl－tetrahydropalmatine on the locomotor activity produced by BEN/LD in rats. Data presented as group means±SE of 6 rats for each group.THP＝dl－detrahydropalmatine (10 mg/kg, 10 mins prior to testing), BEN/LD＝benserazide (50 mg/kg, 80 mins prior to testing), plus L－dopa (200 mg/kg, 50 mins prior to testing), BEN/LD＋THP＝benserazide and L－dopa pretreatment plus dl－tetrahydropalmatine (n＝6/group).**significantly different from BEN/LD group ($p<0.01$, Duncan's multiple range test).

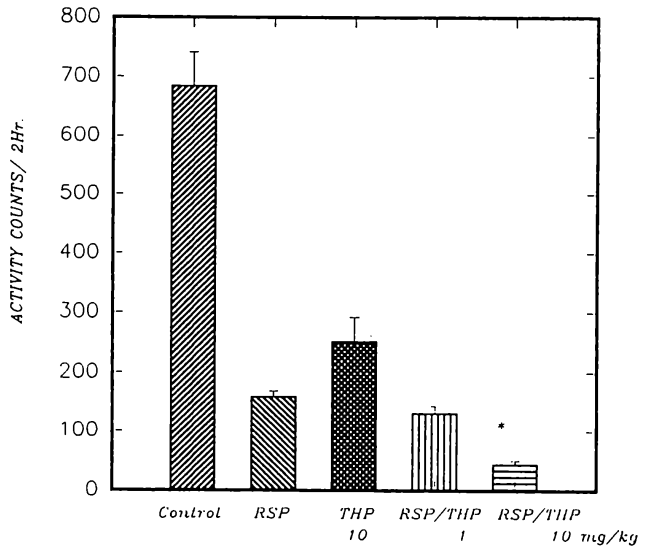

Fig 6. Effect of dl－tetrahydropalmatine on the locomotor activity produced by RSP in rats. Data presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (1,10 mg/kg, 10 mins prior to testing), RSP＝reserpine (0.5mg/kg, 18 hrs prior to testing), RSP/THP＝reserpine pretreatment plus dl－tetrahydropalmatine.* significantly different from RSP group (*$p<0.05$, Duncan's multiple range test).

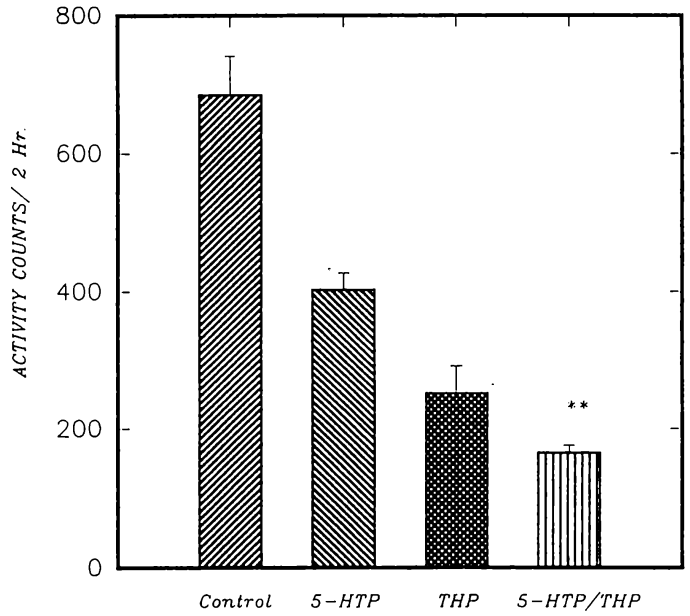

Fig 7. Effect of dl－tetrahydropalmatine on the locomotor activity produced by 5－HTP in rats. DAta presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (10mg/kg, 10 mins prior to testing), 5HTP＝5－hydroxytryptophan (50 mg/kg, 30 mins prior to testing), 5－HTP/THP＝5－hydroxytryptophan pretreatment plus dl－tetrahydropalmatine.** Significantly different from 5－HTP group ($P<0.01$, Duncan's multiple range test).

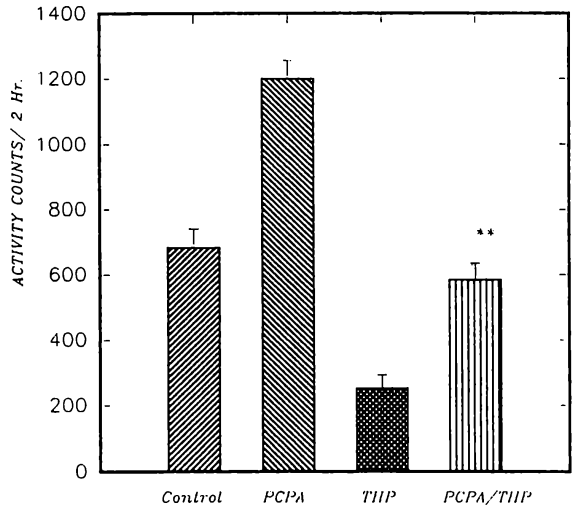

Fig 8. Effect of dl－tetrahydropalmatine on the locomotor activity produced by PCPA in rats. Data presented as group means±SE of 6 rats for each groups. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), PCPA＝p－chlorophenylalanine (200 mg/kg, 24 hrs prior to testing), PCPA/THP＝p－chlorophenylalanine pretreatment plus dl－terahydropalmatine.

**significantly different from PCPA group ($p<0/01$, Duncan's multiple range test).

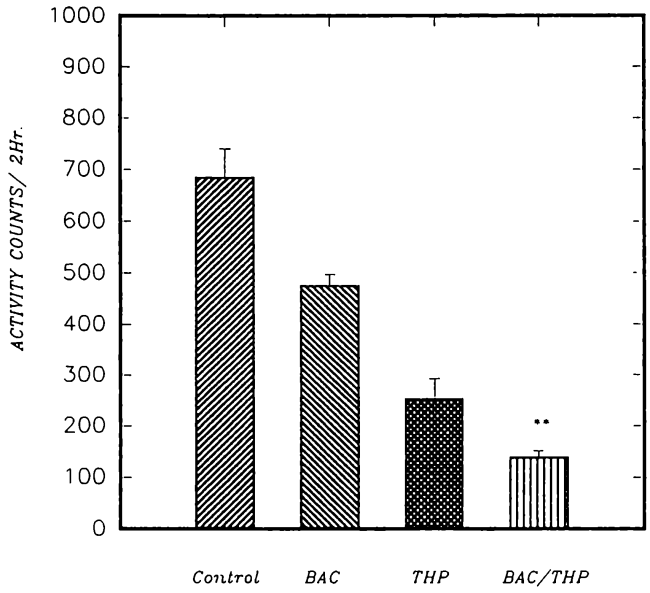

Fig 9. Effect of dl－tetrahydropalmatine on the locomotor activity produced by BAC in rats. Data presented as group means±SE of 6 rats for each groups. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), BAC＝0.5mg/kg baclofen 10 mins prior to testing, BAC/THP＝baclofen pretreatment plus dl－tetrahydropalmatine.** Significantly different from BAC group ($P<0.01$, Duncan's multiple range test).

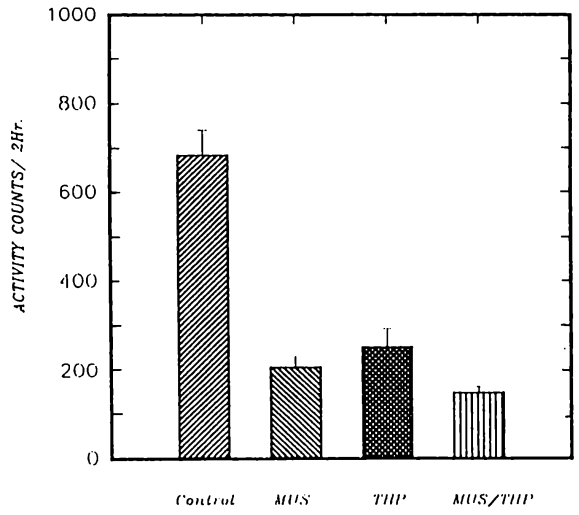

Fig 10. Effect of dl－tetrahydropalmatine on the locomotor activity produced by MUS in rats. Data presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), MUS＝muscinol (0.5 mg/kg, 10 mins prior to testing), MUS/THP＝muscimol pretreatment plus dl－tetrahydropalmatine (n＝6/group).

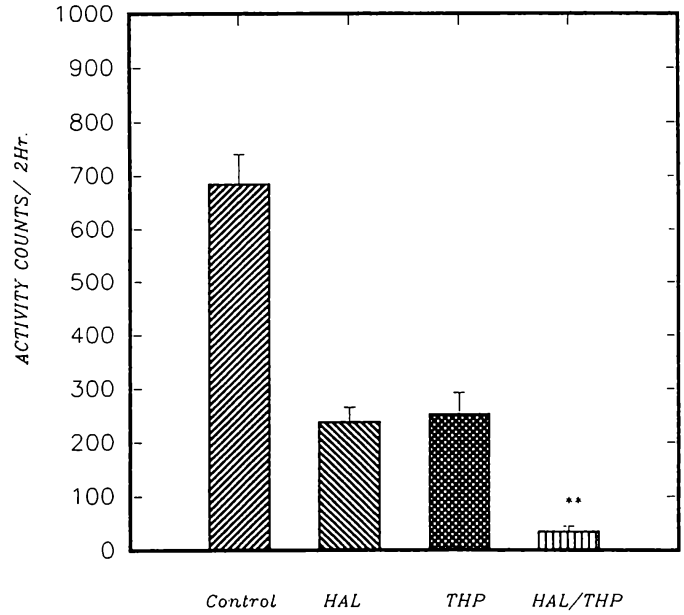

Fig 11. Effect of dl－tetrahydropalmatine on the locomotor activity produced by HAL in rats. Data presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), HAL＝haloperidol (0.001 mg/kg, 30 mins prior to testing), HAL/THP＝haloperiodol pretreatment plus dl－tetrahydropalmatine.** signifificantly different from HAL group ($p<0.01$, Duncan's multiple range test).

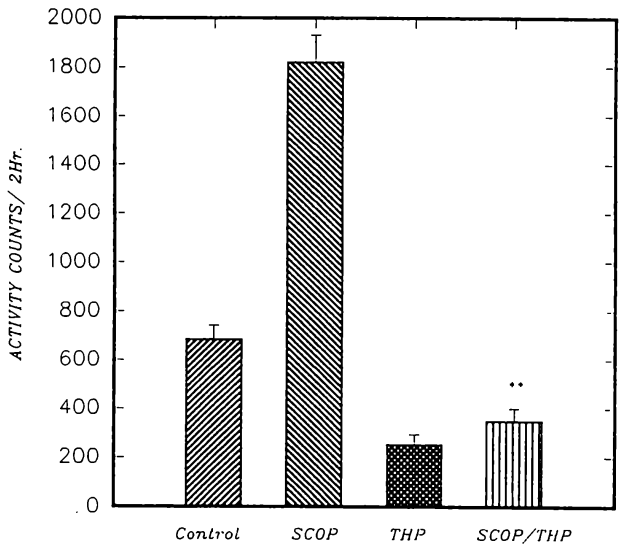

Fig 12. Effect of dl－tetrahydropalmatine on the locomotor activity produced by SCOP in rats. Data presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (10 mg/kg, 10 mins prior to testing), SCOP＝scopolamine (0.5 mg/kg, 30 mins prior to testing), SCOP/THP＝scopolamine pretreatment plus dl－tetrahydropalmatine.** Significantly different from SCOP group ($p<0.01$, Duncan's multiple range test).

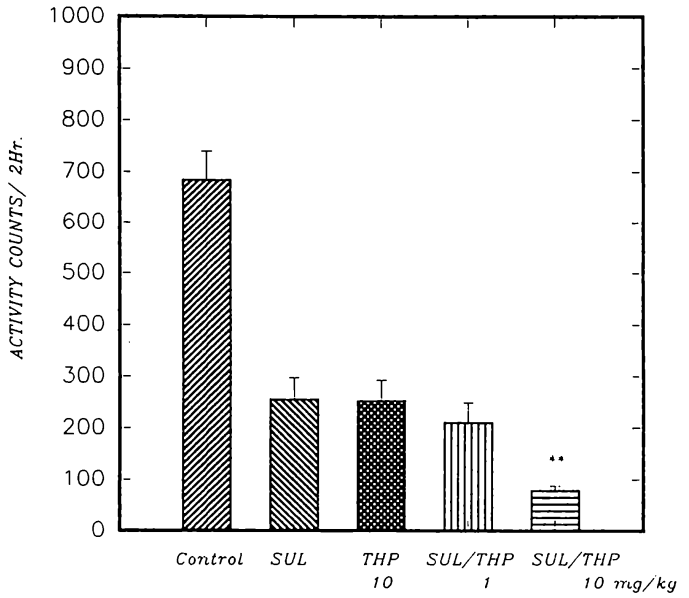

Fig 13. Effect of dl－tetrahydropalmatine on the locomotor activity produced by SUL in rats. Data presented as group means±SE of 6 rats for each group. THP＝dl－tetrahydropalmatine (1,10 mg/kg, 10 mins prior to testing), SUL＝sulpiride (20 mg/kg, 30 mins prior to testing), SUL/THP＝sulpiride pretreatment plus dl－tetrahydropalmatine.** Significantly different from SUL group ($p<0.01$, Duncan's multiple range test).

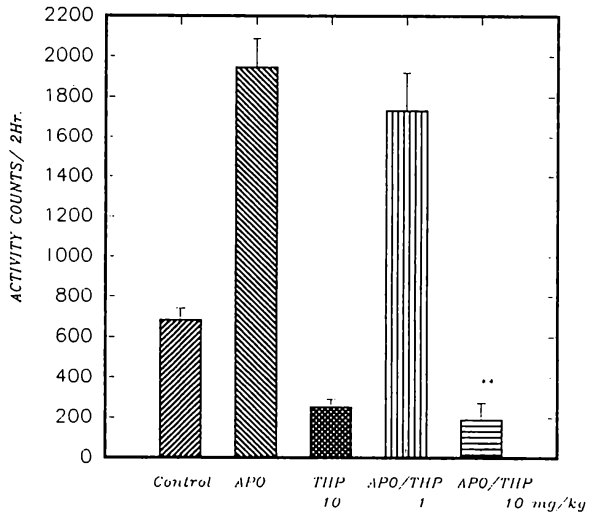

Fig 14. Effect of dl－tetrahydropalmatine on the locomotor activity produced by APO in rats. Data presented as group means±SE of 6 rats for each group. THP＝1,10 mg/kg dl－tetrahydropalmatine (10 mins prior to testing), APO＝1 mg/kg apomorphine (15 mins prior to testing), APO/THP＝apomorphine pretreatment plus dl－tetrahydropalmatine.** significantly different from APO group ($p<0.01$, Duncan's multiple range test).

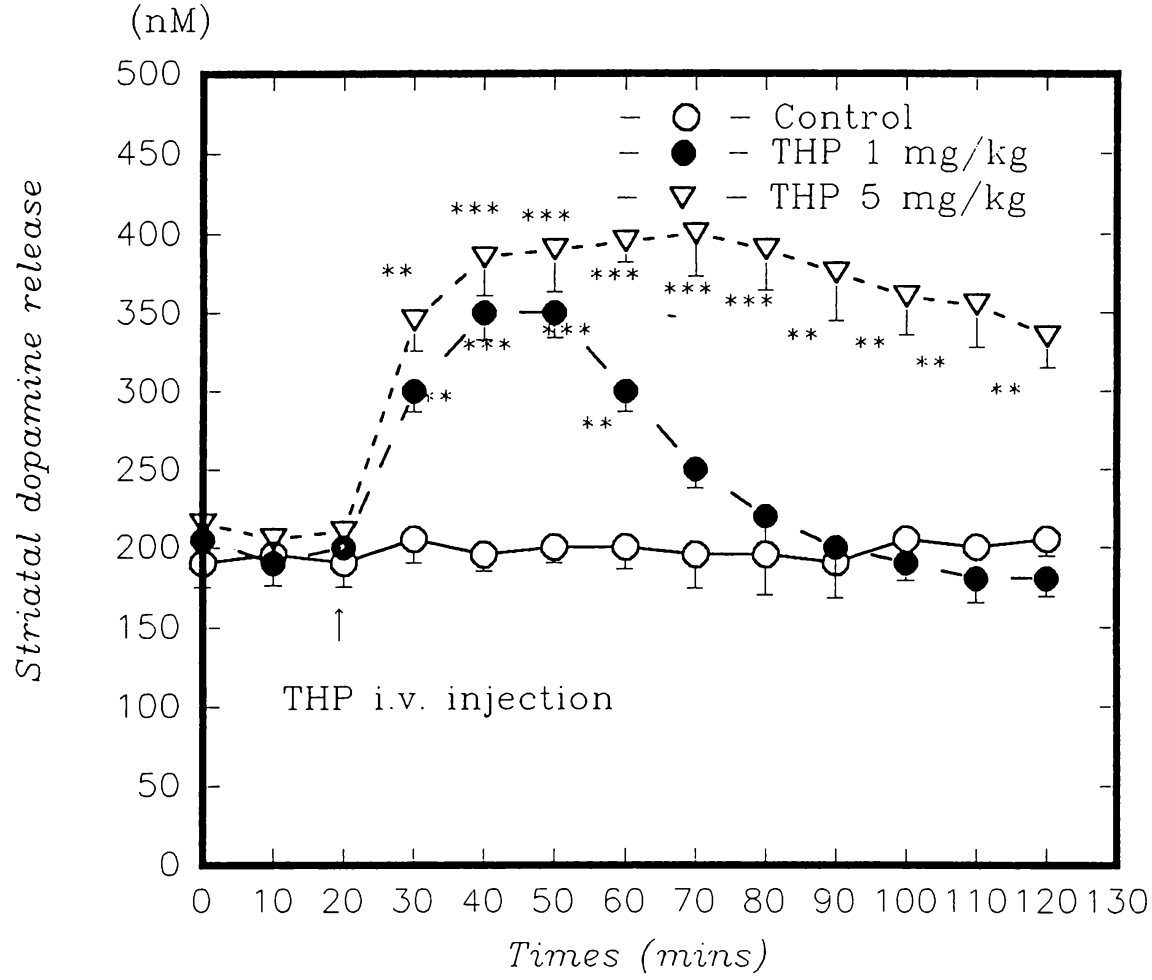

Fig 15. Effects of intravenous administration of dl－tetrahydropalmatine (THP) on striatal dopamine release in rats. Data are presented as mean±SE* significantly different from control group (**P<0.01,***P<0.001; student's T－test)

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A Study on the Sedative Effect of DL—Tetrahydropalmatine —— An Active Principle of Corydalis Tuber

Ming-chun Hsieh and Wen-huang Peng

Research Institute of Chinese Pharmaceutical Sciences, China Medical College

ABSTRACT

Dl-tetrahydropalmatine (THP) is one of the active principles of Corydalis Tuber, which possesses sedative and hypnotic effects. According to Kuo-ching Liu THP was a short-term monoamine depleting constituent. But Liu did not investigate the effect of THP on the dopamine receptor. Hence, this study used behavioral pharmacology, biochemistry and voltammetry together with dopamine receptor agonist and antagonist to determine the action mechanism and action site of this constituent.

The results of this study showed that with the increase of dosage, THP markedly inhibited the amount of the rat's automotor activity and it also produced rigidity in a comparatively higher dose (20 mg/kg). In the dose of 10 mg/kg, it inhibited the amount of motor activity induced by the catecholamine synthesis inhibitor α-MT, the depleting agent reserpine, the antagonist of the mixture of D_1 and D_2 haloperidol, the D_2 antagonist sulpiride, the serotonine precursor 5-HTP, and the GABA agonist baclofen. It could also inhibit the increased motor activity induced by the combination of the dopamine precursor L-dopa and the dopa decarboxylase inhibitor benserazide, the D_2 agonist apomorphine, the acetylcholine blocking agent scopolamine, and the serotonine synthesis inhibitor PCPA. These evidences showed that the sedative and hypnotic effects of THP might have connection with the monoamine system and the GABAergic system of the brain.

Investigation using the biochemical method (HPLC) into the effect of THP on the monoamine concentration in the rat's brain showed that with the increase of THP doses, the norepinephrine and dopamine concentration in the cerebral cortex and brain stem were markedly reduced and the dopamine metabolite HVA was increased. In comparatively higher doses (20 mg/kg), it reduced the cortical 5-HT concentration and increased the concentration of its metabolite 5-HIAA. These

results showed that the sedative and hypnotic effects of THP were probably associated with THP's effects ineducing the dopaminergic acticity of the cerbral cortex and brain stem, and the rigidity effect produced in higher doses might be related to THP'S effects in inhibiting the cortical and brain-stem dopamine and reducing cortical 5-HT concentration.

The voltammetric method used in exploring the THP effect on dopamine release in the corpus striatum of the rat's brain showed that in low doses THP markedly increased the dopamine release in the rat's corpus striatum and the release is augmented with increase in THP doses. With this evidence together with the fact that THP could inhibit the function of the cerebral dopamine system, it followed that the sedative and hypnotic effects of THP were chiefly due to THP's action on the neuron of the dopamine receptor in the cerebral corpus striatum, blockage of the postsynapse of the dopamine receptor, and the feedback action on the presynaptic D_2 receptor to increase dopamine release.

To summarize, the sedative and hypnotic as well as the rigidity effects of THP were chiefly due to its action on the dopamine-acetylcholine-GABA-dopamine nervous loop in the corpus striatum and black matter, action on the neuron of the dopamine receptor, blockage of the postsynapse of the dopamine receptor and feedback action on the presynaptic D_2 receptor to increase dopamine release. In addition, rigidity was also subjected to the regulation of 5-HT.